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Dopamine D1-like receptor agonists impair responding for conditioned reward in rats

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The dopamine (DA) D1-like receptor agonist SKF 38393 has been reported to impair responding for conditioned reward. SKF 38393 is a partial agonist and it is possible that the impairment occurred because it prevented endogenous DA from having its full impact on the D1-like receptor. The present experiments evaluated this possibility by examining the effects of several D1-like agonists with differing efficacy at stimulating adenylate cyclase. Male rats ($n=203$) were trained in a procedure with three distinct phases. During the pre-exposure phase the rats were exposed for five 40 min sessions to an operant chamber containing two levers; one produced a lights-off and the other a tone stimulus (3 s). This was followed by the conditioning phase, four sessions during which the levers were removed and the rats received pairings of the lights-off stimulus (80 per day) with food, presented according to a variable time 45 s schedule. The test phase included two sessions during which the levers were present and the number of responses made on each lever was calculated as a ratio of the number of responses made during pre-exposure. Drugs were administered prior to each test session. No-injection and saline groups showed a higher ratio of responding for the lights-off than the tone stimulus, indicating that the lights-off stimulus had become a conditioned reward. The full D1-like agonist SKF 82958 (0.01–1.0 mg/kg, s.c.) and the partial agonists SKF 81297 (0.01–1.0 mg/kg), SKF 77434 (0.01–5.0 mg/kg) and CY 208–243 (0.01–1.0 mg/kg) impaired responding for conditioned reward at one or more of the highest doses. Results suggest that the impairments previously seen with SKF 38393 are not attributable to the partial agonist action of that drug, and continue to support the hypothesis that responding for conditioned reward is dependent on a reward-related DA signal at the D1-like receptor.

Keywords: Conditioned reward – CY 208-243 – D1 receptors – Dopamine – Rat – SKF 77434 – SKF 81297 – SKF 82958

INTRODUCTION

Since Hill (1970) originally showed that responding for conditioned reward was enhanced in rats treated with the dopamine (DA) releaser pipradol (Scheel-Krüger, 1971), there have been many studies evaluating the effects of dopaminergic agents in this paradigm (see Beninger and Ranaldi, 1994 for review). The results have revealed a number of interesting dissociations.

One dissociation was between the effects of systemically administered amphetamine versus apomorphine. The DA releaser and uptake blocker amphetamine (Scheel-Krüger, 1971; Westerink, 1979; Grace, 1991) enhanced responding for conditioned reward in a dose-dependent manner (Robbins *et al.*, 1983; Beninger *et al.*, 1989; Cohen and Branch, 1991; Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1993; Ranaldi *et al.*, 1995). On the other hand, the direct acting DA agonist apomorphine (Colpaert *et al.*, 1976) enhanced lever pressing but responding was not specifically directed towards the lever that produced the conditioned rewarding stimulus (Robbins *et al.*, 1983; Beninger and Ranaldi, 1992). One interpretation of these findings, previously discussed by others (Herberg *et al.*, 1976; Robbins and Everitt, 1982; Robbins *et al.*, 1983; Beninger *et al.*, 1989; Beninger and Ranaldi, 1992), follows from the observation that there is a burst of activity in DA neurons associated with the presentation of a primary or conditioned rewarding stimulus (Radhakishun *et al.*, 1988; Phillips *et al.*, 1992; Schultz *et al.*, 1993). Amphetamine, by enhancing the release of DA (Grace, 1991), would enhance the reward signal and therefore augment responding for conditioned reward. Apomorphine, by directly stimulating DA receptors, would mask the DA signal associated with reward; motor stimulation would result but the control of responding by reward would be lost, accounting for the indiscriminate increase in responding both on a lever that produced conditioned reward and on a control lever that did not (for a more detailed discussion see Miller *et al.*, 1990; Beninger and Ranaldi, 1994).

Another dissociation was found between the effects of systemically administered agonists acting specifically at

DA receptor subtypes. At least five major DA receptor subtypes have been identified in recent years but there remain two distinct classes, D1- and D2-like receptors, based on their ability to stimulate and inhibit, respectively, the enzyme adenylate cyclase (Niznik and Van Tol, 1992; Civelli *et al.*, 1993; Sibley *et al.*, 1993). In studies of the acquisition of responding for conditioned reward, it was found that the D2-like agonists quinpirole (Tsuruta *et al.*, 1981) and bromocriptine (Markstein, 1981) dose-dependently enhanced responding specifically on a lever producing conditioned reward (Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1995). The D1-like agonist SKF 38393 (Setler *et al.*, 1978), on the other hand, dose-dependently impaired responding for conditioned reward (Beninger and Ranaldi, 1992; Ranaldi *et al.*, 1995). When considered along with the observation that the directly acting DA agonist apomorphine, known to stimulate both D1-like and D2-like receptors, impaired responding for conditioned reward, these results were taken to suggest that the critical site of action for the putative DA signal associated with reward was the D1 receptor (Beninger, 1991, 1993).

An alternative possibility is that the impairment of responding for conditioned reward produced by SKF 38393 is related to the pharmacological properties of this drug. Thus, SKF 38393 is a partial agonist at D1-like receptors, stimulating adenylate cyclase to a maximum of 45–70% of the level produced by DA itself (Setler *et al.*, 1978; Andersen *et al.*, 1985; Arnt *et al.*, 1988). Perhaps SKF 38393 impaired responding for conditioned reward because its occupancy of D1-like receptors partially antagonized endogenous DA from producing its maximal effect. The present studies tested this possibility by evaluating the effects on responding for conditioned reward of several D1-like receptor agonists with different efficacies at stimulating adenylate cyclase.

The D1-like agonists included SKF 82958, SKF 81297, SKF 77434 and CY 208-243. SKF 82958 has been reported to be a full agonist, stimulating adenylate cyclase with an efficacy greater than that of DA (O'Boyle *et al.*, 1989). SKF 81297 is a high efficacy agonist, often referred to as a full agonist, stimulating adenylate cyclase activity with an efficacy of 68–88% (Andersen and Jansen, 1990; Arnt *et al.*, 1992). SKF 77434 was found to be a partial agonist, having an efficacy relative to DA of about 48% (O'Boyle *et al.*, 1989). SKF 38393 and the SKF compounds mentioned above are all 1-phenyl-1H-3-benzazepine derivatives. The D1-like agonist CY 208-243 is a phenanthridine derivative that is structurally unrelated to the SKF compounds but also has been shown to be a partial agonist with an efficacy at D1-like receptors of 63% (Markstein *et al.*, 1988); however, the specificity of CY 208-243 for D1-like receptors has been questioned (Andersen and Jansen, 1990).

METHODS

Subjects

Treatment of the rats in the present study was in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant University policy, and was approved by the Queen's University Animal Care Committee.

Male Wistar rats ($n = 203$), obtained from Charles River Canada, weighing between 200 and 250 g (free-feeding), were individually housed in a temperature-controlled environment (21°) on a 12 h light-dark cycle (lights on at 06.00 h). Rats were habituated to the housing environment for approximately one week, during which their weights increased by 25–40 g. Weights were then reduced to 80% of these values for the 11-day duration of the experiment, through daily feeding with measured rations of laboratory chow.

Apparatus

The experimental environment consisted of four similarly constructed operant chambers, 29 cm long, 23 cm wide and 19 cm high. The chambers were constructed of aluminum sides and plexiglass tops and doors, with aluminum grid floors. Each chamber was placed in a ventilated sound-attenuating box. Each 29 cm wall of each chamber contained a 7.5 cm × 3.5 cm removable lever, depression of which required a force of approximately 0.09 N. At the center of the 23 cm wall was located a 2.0 × 4.0 cm feeder cup at a height of 2.5 cm from the floor. An illuminated 2 W bulb was positioned on each side (8.5 cm apart) of the feeder cup at a height of 10 cm from the floor. Each chamber also contained a 4.9 kHz tone generator positioned 14 cm from the floor, between the two light bulbs and at the center of the 23 cm wall. The tone generator was adjusted to deliver a tone 10 dB above the background noise level.

Procedure

Each group was exposed for a total of 11 days to an experimental design that consisted of three distinct phases referred to as pre-exposure, conditioning and test. Sessions occurred during the light portion of the light-dark cycle at about the same time each day.

The pre-exposure phase consisted of five 40 min sessions held at approximately the same time on each of the first five days. Two levers were present: one produced the tone and the other the lights-off stimulus, both lasting 3 s. Two of the chambers had the tone-producing lever on the right wall and the lights-off-producing lever on the left wall; the relationship between lever side and stimulus was reversed for the other chambers. The number of

responses on each lever was measured for each pre-exposure session.

The conditioning phase consisted of 60 min sessions held on each of the next four days. Both levers were removed from the operant chambers and the rats were exposed to 80 presentations of the 3 s lights-off stimulus according to a random time 45 s schedule, the mean time between lights-off stimulus presentations being 45 s (range 5–90 s). During the first conditioning session, each lights-off stimulus presentation was terminated with the delivery of one 45 mg food pellet (Bioserv). During the remaining conditioning sessions, food delivery occurred following a random 33% of the lights-off stimuli. This procedure was employed because partial pairing has been reported to produce a greater magnitude of conditioned reward than continuous pairing (Knott and Clayton, 1966).

The test phase consisted of two 40 min sessions held on the next two days. The levers again were present in the operant chambers and they produced the same stimuli as in the pre-exposure phase. Conditioned reward was observed as a relative increase in the number of responses on the lights-off versus the tone lever in the test compared to the pre-exposure phase.

A total of 16 groups was tested. One control group ($n = 13$) received no injections prior to any phase of the experiment. A second control group ($n = 14$) received saline (1 ml/kg) 15 min prior to each test session. Three groups ($n = 12$, 12 and 21) received SKF 82958, three groups ($n = 12$, 12 and 16) received SKF 81297, and three groups ($ns = 10$) received CY 208-243, in doses of 0.01, 0.1 and 1.0 mg/kg, s.c.; SKF 82958 and SKF 81297 were injected 15 min prior to each test session and CY 208-243 was injected immediately prior to each test session. Five groups ($n = 12$, 11, 13, 13 and 12) received SKF 77434 at the same doses as the other drugs plus doses of 2.5 and 5.0 mg/kg, s.c., injected 15 min prior to test sessions.

Drugs

SKF 82958 (3-allyl-6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine), SKF 81297 (2,3,4,5-tetrahydro-6-chloro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine), and SKF 77434 (3-allyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1H-3-benzazepine) were purchased from Research Biochemicals International (Natick, MA). CY 208-243 ([-]-4,6,6a,7,8,12b-hexahydro-7-methylindolo[4,3-ab]phenanthridine) was a gift from Sandoz, Basel. All drugs were dissolved in distilled water and were prepared daily for injection in a concentration of 1 ml/kg.

Data analyses

The data from the last 30 min provided the most stable estimate of pre-exposure response rates. In previous studies (Hoffman and Beninger, 1985) the number of responses in each 10 min segment of 40 min pre-exposure sessions was analyzed and it was found that rates were higher in the first 10 min but did not differ significantly for the remaining 10 min periods. Therefore, only data from the last 30 min of the session were used in the analyses of the present results. The number of responses made on each lever during the last 30 min of the five pre-exposure sessions was averaged for each rat. Similarly, the number of responses made on each lever during the last 30 min of each test session was averaged for each rat. Finally, the mean number of responses on each lever in the test phase was divided by the mean number of responses on that lever in the pre-exposure phase, adding 1.0 to each value entering into the ratio to reduce the influence of numerically small numbers (Winer, 1962). These ratios were then transformed to square root values to normalize their distribution for the purposes of analyses (Keppel, 1982). Thus, the data consisted of two numbers for each rat.

To evaluate the conditioned reward effect in the no-injection and vehicle control groups, a two-way mixed design analysis of variance (ANOVA), with repeated measures on the lever variable and independent groups, was carried out. A significantly higher ratio of responding on the lights-off lever than on the tone lever was taken as evidence that conditioned reward had occurred. The results of groups receiving each drug were similarly subjected to two-way ANOVAs with repeated measures on the lever factor, and independent groups; each of these ANOVAs included the control group as a treatment dose of 0 mg/kg. These ANOVAs were followed by planned comparisons of the lever effect for each dose of each D1-like receptor agonist.

RESULTS

For both the no-injection and the saline control groups, in the pre-exposure phase, the mean number of responses on the tone and lights-off levers was about the same, although the means differed somewhat between experiments (Table I). In the test phase, both groups showed little change in responding on the tone lever, while responses more than doubled on the lights-off lever. When the square root ratios for the lever producing each stimulus for each control group were assessed, ANOVA revealed a significant lever effect [$F(1,25) = 16.9$, $p < 0.001$]. As there was no significant main effect of group or interaction, the data for these two groups were combined and the single control group was used as the 0 mg/kg treatment in the ANOVAs for each drug.

TABLE I. Mean (±SEM) pre-exposure and test number of responses, ratio and square-root-transformed ratio values, for each lever for the no-injection and saline groups alone and in combination[1]

		Pre-exposure		Test		Ratio		Sq root	
Group	*n*	Tone	L-O	Tone	L-O	Tone	L-O	Tone	L-O
No-injection	13	12.4 ±4.5	11.7 ±2.4	12.6 ±2.7	32.2 ±6.3	1.5 ±0.3	4.0 ±1.2	1.1 ±0.1	1.8* ±0.3
Saline	14	8.6 ±0.9	6.8 ±1.3	9.3 ±3.0	16.1 ±3.7	1.0 ±0.3	3.8 ±1.5	0.9 ±0.1	1.7* ±0.3
Combination	27	10.5 ±2.2	9.1 ±1.4	10.8 ±2.0	23.5 ±3.8	1.3 ±0.2	3.9 ±0.9	1.0 ±0.1	1.7† ±0.2

[1]Abbreviations: L-O; lights-off lever
*different from tone lever in a *t*-test, $p < 0.01$
†different from tone lever in ANOVA, $p < 0.001$

Each of the D1-like receptor agonists impaired selective responding for the food-associated stimulus at one or more doses (Fig. 1). The full agonist SKF 82958 appeared to be most potent, blocking differential responding for the lights-off stimulus at a minimum dose of 0.1 mg/kg. For SKF 81297 and CY 208-243, an impairment was seen only at the 1.0 mg/kg dose. SKF 77434 was least potent, a dose of 5.0 mg/kg being required to impair differential responding for the lights-off stimulus. Statistical analysis confirmed this description of the data.

The ANOVA for groups receiving control treatments or SKF 82958 revealed a significant lever by treatment interaction, [$F(3,68) = 4.7, p < 0.005$]. As described above, the lever effect for the control group was significant. Planned comparisons of the mean ratios for each lever at each dose revealed a significant effect for 0.01 mg/kg [$t(11) = 3.11$, $p = 0.01$] but not for 0.1 or 1.0 mg/kg [$t(11$ and $20) < 1.0$, NS]. Thus, the differential increase in responding for the lights-off stimulus was impaired by the two higher doses.

The ANOVA for the control group plus the doses of SKF 81297 also revealed a significant lever by treatment interaction [$F(3,63) = 3.0$, $p < 0.05$]. Planned comparisons of the lever effect for each treatment revealed a significant effect in the 0.01 and 0.1 mg/kg dose groups [$t(11) = 4.0$ and 3.6, respectively, $p < 0.005$], but not in the 1.0 mg/kg dose group [$t(15) = 1.1$, NS]. Thus, the 1.0 but not the 0.1 or 0.01 mg/kg doses of SKF 81297 impaired responding for the food-associated stimulus.

For SKF 77434, the ANOVA revealed a significant lever effect [$F(1,82) = 19.6$, $p < 0.001$], but a nonsignificant lever by treatment interaction [$F(5,82) = 2.1$, $p = 0.08$]. Planned comparisons revealed a significantly greater increase in responding on the lights-off lever in the group receiving 0.01 mg/kg [$t(11) = 2.3$, $p < 0.05$]. The groups receiving 1.0 or 2.5 mg/kg SKF 77434 showed a significant lever effect according to a one-tailed test, the hypothesis for this test being that a greater ratio of responding would be seen on the lights-off lever [$t(12) = 1.9$ and 1.8, $p < 0.05$]. For the 0.1 mg/kg dose the one-tailed test revealed a nonsignificant lever effect [$t(10) = 1.6$, $p = 0.07$]. No evidence of greater responding on the lights-off lever was seen in the group receiving 5.0 mg/kg [$t(11) < 1.0$, NS]. In summary, the group receiving 0.01 mg/kg of SKF 77434 showed a clear increase in responding on the lights-off lever and the group receiving 5.0 mg/kg clearly did not. Groups receiving doses within this range showed some evidence of a differential increase, suggesting that SKF 77434 doses of 0.1, 1.0 and 2.5 mg/kg may have weakened the effect.

Groups receiving CY 208-243, when subjected to ANOVA along with the control group, showed significant lever and treatment effects [$F(1,53) = 19.7, p < 0.001$ and $F(3,53) = 5.1, p < 0.005$, respectively], but no significant interaction. Multiple comparisons revealed that the treatment effect occurred because the group receiving 0.1 mg/kg responded more on both levers combined in the test phase than did the control group or the groups receiving the other two doses of CY 208-243. Planned comparisons of the ratios for the two levers for each group revealed a significant lever effect in the groups receiving 0.01 and 0.1 mg/kg [$t(9) = 2.5$ and 2.4, $p < 0.05$], but not in the group receiving 1.0 mg/kg [$t(9) < 1.0$, NS]. Thus, CY 208-243 dose-dependently impaired differential responding for the lights-off stimulus in the test phase.

DISCUSSION

The data can be summarized as follows: each of the D1-like agonists SKF 82958, SKF 81297, SKF 77434 and CY 208-243, at one or more doses, impaired differential responding on a lever that produced a stimulus that previously had been paired with food, relative to a lever that produced a stimulus not previously paired with food. Control animals receiving no injection or saline injections

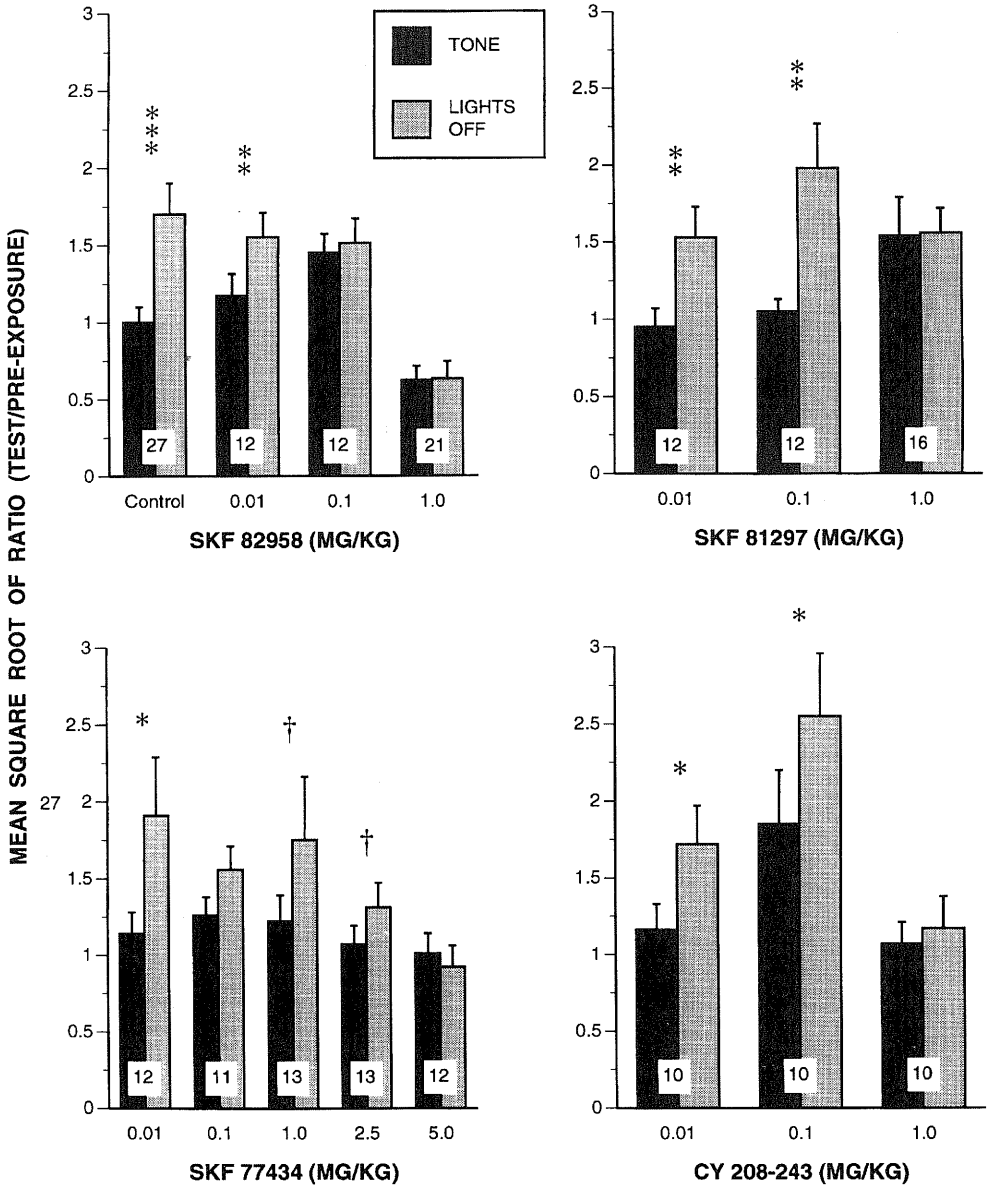

FIG. 1. Mean (+SEM) square root of ratios of responding on the tone and lights-off levers (test/pre-exposure) for animals treated with varying doses of SKF 82958, SKF 81297, SKF 77434 or CY 208-243. Numbers in each pair of bars indicate numbers of animals tested. Significant lever effect by planned *t*-test: ***$p <$ LT:0.001; **$p < 0.01$; *$p < 0.05$; †$p < 0.05$, one-tailed test.

prior to test sessions, and animals receiving low doses of the D1-like agonists, showed a significantly greater increase in responding on the lever producing the stimulus previously paired with food. These latter observations are taken as evidence that the lights-off stimulus had become a conditioned reward as a result of being paired with food in the conditioning phase. Thus, D1-like agonists, at one or more of the higher doses given, impaired responding for conditioned reward.

The conditioning phase involved a classical conditioning procedure. Typically, control groups are included in classical conditioning experiments to confirm that an association is being learned between the unconditioned and conditioned stimulus (Mackintosh, 1974). Although such control groups were not included in the present experiment, previous studies from this lab using the same apparatus and procedure have included control groups that confirm that the relative increase in responding on the lights-off versus the tone lever in the test phase is a conditioned reward effect. Thus, when food and the lights-off stimulus were negatively correlated in the conditioning phase (Hoffman and Beninger, 1985) or when food alone was presented in the conditioning phase (Beninger and Ranaldi, 1992), responding on the lights-off

and tone levers in the test phase did not differ significantly.

In a previous study, the ability of the tone to act as a conditioned reward was examined by pairing the tone with food in the conditioning phase (Beninger and Ranaldi, 1992). The results revealed a small but non-significant increase in responding on the tone lever in the test; however, in a group that received amphetamine in the test, a significant enhancement of responding on the tone lever was seen. This finding was consistent with our previous observations (unpublished) that better conditioned reward effects were seen with the lights-off than with the tone stimulus. Whether this is related to the specific frequency and intensity of the tone employed here, or to differences in the efficacy of auditory versus visual stimuli to act as conditioned rewards when paired with food, awaits further study. For the present purposes, pairing of the lights-off stimulus with food appears to lead to the lights-off stimulus acting as a conditioned reward. This provides a reliable paradigm for examining the possibility that the disruption of conditioned reward produced by D1-like agonists is related to their efficacy at the D1-like receptor.

Previous studies have shown that the D1-like agonist SKF 38393, injected during the test phase, impaired responding for conditioned reward (Beninger and Ranaldi, 1992; Ranaldi *et al.*, 1995). The present study examined the possibility that this impairment may be related to the partial efficacy of SKF 38393 at the D1-like receptor (Setler *et al.*, 1978; Andersen *et al.*, 1985; Arnt *et al.*, 1988); perhaps an impairment was seen because SKF 38393, by occupying D1-like receptors, prevented endogenous DA from fully stimulating adenylate cyclase. The present findings would seem to rule out this possibility. Thus, the full D1-like agonist SKF 82958 (O'Boyle *et al.*, 1989), like the partial D1-like receptor agonists SKF 81297 (Arnt *et al.*, 1992), SKF 77434 (O'Boyle *et al.*, 1989) and CY 208-243 (Markstein *et al.*, 1988), impaired responding for conditioned reward at one or more of the higher doses given. The full agonist SKF 82958 appeared to be more potent than the structurally related partial agonists SKF 81297 and SKF 77434, producing a clear impairment of responding for conditioned reward at a dose of 0.1 mg/kg. Thus, the impairment of responding for conditioned reward produced by SKF 38393 does not appear to be attributable to its mechanism of action as a partial agonist at the D1-like receptor.

The findings that D1-like agonists, at higher doses, impaired responding for conditioned reward (present results; Beninger and Ranaldi, 1992; Ranaldi *et al.*, 1995) and that D2-like agonists enhanced responding for conditioned reward (Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1995) continue to support the hypothesis that a burst of activity in DA neurons, the DA signal, associated with the presentation of conditioned reward (Radhakishun *et al.*, 1988; Phillips *et al.*, 1992; Schultz *et al.*, 1993), acts critically at the D1-like receptor to produce reward-related incentive learning, i.e., to enhance the ability of the lever and lever-related stimuli to control responding (Beninger, 1983, 1991, 1993; Miller *et al.*, 1990). From this point of view, the enhanced stimulation of D1-like receptors produced by D1-like agonists in the test phase of the conditioned reward experiments leads to a masking of the DA signal associated with reward and a loss of control of responding by the lever and lever-related stimuli.

There are some data that may appear to contradict this model. In one recent study, intra-accumbens injections of SKF 38393, similarly to D2-like agonists or amphetamine, enhanced responding for conditioned reward (Wolterink *et al.*, 1993). In a related study, however, intra-accumbens injections of CY 208-243 failed to affect responding for conditioned reward although co-injection with a D2-like agonist produced an enhancement (Chu and Kelley, 1992). In another report, moderate doses of DA itself injected into the nucleus accumbens enhanced responding for conditioned reward (Cador *et al.*, 1991). If the DA signal at D1-like receptors in the nucleus accumbens was critical for reward-related learning, it might be expected that direct stimulation of D1-like receptors with D1-like agonists or DA would mask the signal. As we have suggested elsewhere (Beninger and Ranaldi, 1994), perhaps the DA signal is distributed to the accumbens and other structures; if so, systemic treatments might mask the signal whereas local treatments might not. This account is consistent with the observation of enhanced responding for conditioned reward following central injections of a D1-like agonist (Wolterink *et al.*, 1993) but impaired responding following systemic treatments with D1-like agonists (present results; Beninger and Ranaldi, 1992; Ranaldi *et al.*, 1995).

An alternative interpretation of the present results is that systemically injected D1-like agonists failed to penetrate the brain adequately, especially the nucleus accumbens. This may have led to the failure to see an enhancement of responding for conditioned reward like that seen with intra-accumbens injections of some D1-like agonists (Wolterink *et al.*, 1993). However, this possibility seems unlikely, as there is ample evidence that D1-like agonists do penetrate the brain. For example, a recent study showed that grooming induced by SKF 38393 was antagonized by irreversible inactivation of D1-like receptors in a region of the striatum (Neisewander *et al.*, 1995). This finding suggests that SKF 38393 acted on D1-like receptors in that region to produce its behavioral effects. In another study, an oligodeoxynucleotide antisense to D1 receptor mRNA, injected intracerebroventricularly, inhibited behaviors induced by

systemically injected D1-like agonists (Zhang *et al.*, 1994), suggesting that the D1-like agonists acted centrally. Robertson and Jian (1995) reported that systemic injection of CY 208-243 enhanced Fos-like immunoreactivity in dopaminoceptive projection neurons of the nucleus accumbens; this finding shows that a systemically administered D1-like agonist penetrated the nucleus accumbens and acted on D1-like receptors there to enhance levels of a protein normally synthesized as a result of D1-like receptor stimulation. These results make it unlikely that the discrepancy between the present findings and those of Wolterink *et al.* (1993) can be attributed to inadequate penetration of systemically injected D1-like agonists into the brain.

Some studies have evaluated the effects of D1-like agonists on responding for brain stimulation reward (BSR); results have not been consistent. It was found that systemic treatments with the full D1-like receptor agonist A-77636 (Kebabian *et al.*, 1992) potentiated responding for BSR (Ranaldi and Beninger, 1994), shifting the rate-frequency function to the left, but that SKF 38393 had no significant effect (Nakajima and O'Regan, 1991) or impaired responding for BSR, shifting reward summation functions to the right (Hunt *et al.*, 1994). BSR produces a sudden and dramatic increase in DA release (Phillips *et al.*, 1989), possibly leading to a powerful reward signal that may be resistant to the putative masking effects of D1-like agonists; this may account for the reward-enhancing effects of A-77636. From this point of view, it is unclear why SKF 38393 would not also enhance reward. It may be that the different efficacies of A-77636 versus SKF 38393 at D1-like receptors influence their effects on reward; however, the present findings suggest that both partial and full D1-like agonists similarly impair responding for conditioned reward. Further studies of the effects of D1-like agonists on responding for BSR are needed.

A number of recent findings are consistent with the impairment in responding for conditioned reward observed in the present experiments. In the self-administration paradigm, very low doses of SKF 82958, SKF 77434 (Self and Stein, 1992) or SKF 81297 (Weed *et al.*, 1993) were rewarding but higher doses failed to maintain responding. It is not easy to compare doses directly across paradigms, but these results are consistent with the suggestion that D1-like agonists impair responding at higher doses. Animals trained to press a lever for food showed a disruption of responding when injected with SKF 38393 (Hoffman and Beninger, 1989; Katz and Witkin, 1993). Although this finding is consistent with the effects of SKF 38393 on responding for conditioned reward, an effect of SKF 38393 on appetite cannot be ruled out (Terry and Katz, 1992). Finally, some studies avoided the possible confounding influence of effects on appetite. Evaluating lever pressing maintained by electric shock in squirrel monkeys, it was found that SKF 38393, SKF 82958, SKF 81297, SKF 77434 and SKF 75670 (3-methyl-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine) impaired responding in a dose-dependent manner (Katz *et al.*, 1995). In squirrel monkeys negatively reinforced for lever pressing on a fixed interval schedule, a number of D1-like agonists impaired responding with increasing dose although CY 208-243, at one dose, enhanced responding (Bergman *et al.*, 1995). Similarly, responding maintained by cocaine self-administration was impaired dose-dependently by SKF 38393 (Katz and Witkin, 1993). These results generally are in good agreement with the present findings.

In conclusion, D1-like receptor agonists, although found to produce rewarding effects in some behavioural paradigms (e.g. self administration, place preference (White *et al.*, 1991)), dose-dependently impair responding maintained by a number of rewarding stimuli including cocaine, food, electric shock and conditioned reward. These impairments may be understood as resulting from a masking of the reward signal that results from the endogenous release of DA when reward is presented. The results support the hypothesis that stimulation of D1-like DA receptors is critical to incentive learning associated with the presentation of rewarding stimuli.

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